Title: Hermansky-Pudlak Syndrome *GeneReview* – Molecular Genetics: Gene Symbol Aliases and Less Common Genes
Authors: Huizing M, Malicdan MCV, Gochuico BR, Gahl WA
Updated: October 2017
Note: The following information is provided by the authors and has not been reviewed by *GeneReviews* staff.

Gene Symbols and Gene Symbol Aliases for Genetic Causes of Hermansky-Pudlak Syndrome

Gene Symbol [1]	Gene Symbol Aliases [2]
AP3B1	*ADTB3, HPS2*
AP3D1	*HPS10, ADTD*
BLOC1S3	*HPS8, RP, BLOS3*
BLOC1S6	*HPS9, PLDN, BLOS6*
DTNBP1	*BLOC1S8, HPS7*
HPS1	*BLOC3S1, HPS*
HPS3	*BLOC2S1*
HPS4	*BLOC3S2*
HPS5	*BLOC2S2*
HPS6	*BLOC2S3*

1. HGNC-approved gene symbols (listed alphabetically)

2. Gene symbol aliases are unapproved nomenclature that may be used in older literature; some are listed at the HGNC.

Less Common Genetic Causes of Hermansky-Pudlak Syndrome

AP3D1

Gene structure. The longest AP3D1 mRNA transcript variant (NM_001261826) consists of 32 exons and has an open reading frame of 3648 bp. For a detailed summary of gene and protein information, see Table A, **Gene**. See above for gene symbol aliases.

Pathogenic variants. As of July 2017, only one pathogenic variant c.3565_3566delGT (p.Val1189Leufs*8) has been reported in a Turkish boy [Ammann et al 2016].

Normal gene product. The product of *AP3D1* is the 1215-amino acid (~136.7 kd) protein AP3D1 (AP-3 δ), which is a subunit of adaptor complex-3 (AP-3) [Dell'Angelica et al 1999, Ammann et al 2016]. AP-3 is a heterotetrameric coat protein complex that

forms intracellular vesicles (presumably lysosomes and lysosome-related organelles, including melanosomes, dense bodies, and lytic granules) from the trans-Golgi network and endosomes in a clathrin-mediated fashion. AP3D1 interacts with three other AP-3 subunits (β, μ and σ) to perform its function [Dell'Angelica et al 1999].

Abnormal gene product. T cells from the *AP3D1*-deficient boy showed significant decreased AP3D1 protein expression compared to healthy control T cells, as well as reduced protein expression levels of other AP-3 subunits (β3A, σ, and μ), consistent with an unstable heterotetramer formation [Ammann et al 2016]. Cytotoxic lymphocytes from the *AP3D1*-deficient boy demonstrated an impaired degranulation response, similar to individuals with pathogenic variants in *AP3B1* [Enders et al 2006, Jessen et al 2013, Ammann et al 2016].

BLOC1S3

Gene structure. *BLOC1S3* has one mRNA transcript (NM_212550), that contains two exons, but the mRNA open reading frame of 609 bp is contained within a single coding exon [Morgan et al 2006]. For a detailed summary of gene and protein information, see Table A, **Gene**. See above for gene symbol aliases.

Pathogenic variants. As of July 2017, only two pathogenic variants in *BLOC1S3* have been identified, both in the homozygous state. Variant c.448delC was identified in six affected individuals of a single consanguineous Pakistani family [Morgan et al 2006], and variant c.131C>A was described in in an Iranian boy [Cullinane et al 2012].

Table 6. *BLOC1S3* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.131C>A	p.Ser44Ter	NM_212550.3 NP_997715.1
c.448delC	p.Gly150ArgfsTer75	

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants. Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The protein encoded by *BLOC1S3* has 202 amino acids (~21.3 kd) and combines with seven other proteins to form BLOC-1 [Falcón-Pérez et al 2002]. The *BLOC1S3* gene product contains an unstructured amino terminal domain followed by an alpha-helical domain. The function of the *BLOC1S3* gene product is unknown; BLOC-1 is hypothesized to regulate SNARE-mediated membrane events, including membrane fusion [Falcón-Pérez et al 2002], membrane-cytoskeleton interactions [Delevoye et al 2016] and endosomal tubule formation [Di Pietro et al 2006, Delevoye et al 2016].

Abnormal gene product. The homozygous c.131C>A pathogenic variant resulted in aberrantly expressed *BLOC1S3* gene product in the patient's melanocytes, which destabilized the BLOC-1 complex and caused mis-trafficking of the melanogenic protein TYRP1, which abnormally accumulated in the Golgi region and cell membrane, resulting in severely reduced pigment production [Cullinane et al 2012].

BLOC1S6

Gene structure. *BLOC1S6* has two main mRNA splice variants; the longest variant 1 (NM_001311255.1) only recently appeared in databases (April 2017), and therefore previous reports of gene structure and pathogenic variants were reported according to mRNA splice variant 2 (NM_012388.3). Variant 1 (open reading frame 534-bp) and variant 2 (open reading frame 519-bp) both have five exons and vary in their 5' UTR and 5' coding region in exon 1, but each starts translation at a different start codon; exons 2-5 are identical in both variants. For a detailed summary of gene and protein information, see Table A, **Gene**. See above for gene symbol aliases.

Pathogenic variants. As of July 2017, only two unrelated individuals of Italian and Pakistani descent have been described, both carrying the same homozygous nonsense pathogenic variant c.232C>T in *BLOC1S6* [Badolato et al 2012, Yousaf et al 2016]. Note that the variant nomenclature is according to NM_012388.3.

Table 7. *BLOC1S6* Pathogenic Variants Discussed in This *GeneReview*

DNA Nucleotide Change	Predicted Protein Change	Reference Sequences
c.232C>T	p.Gln78Ter	NM_012388.3 NP_036520.1

Note on variant classification: Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

Note on nomenclature: *GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

Normal gene product. The *BLOC1S6* protein product is called BLOC1S6 or PLDN (Pallidin) and shares no homology to any known protein. The protein encoded by *BLOC1S6* variant 1 (NM_001311255.1; NP_001298184) has 177 amino acids (~20.3 kd) and variant 2 (NM_012388.3; NP_036520) has 172 amino acids (~19.7 kd). Expression and features of the 172-amino acid protein variant 2 (NP_036520) was previously described [Moriyama & Bonifacino 2002].

The first 60 amino acids give rise to an unstructured protein, followed by two highly α-helical coiled-coil regions (amino acids 60-100 and 109-172). The two coiled-coil regions have been shown to be essential for PLDN to bind to itself and to syntaxin-13, an early endosomal t-SNARE. The *BLOC1S6* gene product also combines with seven other proteins to form BLOC-1 [Falcón-Pérez et al 2002, Moriyama & Bonifacino 2002].

Abnormal gene product. NK cells from the Italian *BLOC1S3*-deficient individual showed defective degranulation and cytolysis, with abnormal lysosomal markers on NK cells [Badolato et al 2012]. Further cellular studies on *BLOC1S6*-deficient human cells are lacking.

DTNBP1

Gene structure. The longest *DTNBP1*transcript variant (NM_032122.4) has ten exons and contains a 1056-bp open reading frame. For a detailed summary of gene and protein information, see Table A, **Gene**. See above for gene symbol aliases.

Pathogenic variants. As of July 2017, only two nonsense variants have been described in three individuals; a 48-year-old Portuguese female [Li et al 2003], a 77 year-old white female [Lowe et al 2013], and a six-year-old Paraguayan boy [Bryan et al 2017].

Normal gene product. *DTNBP1* encodes the protein DTNBP1 (dystrobrevin binding protein 1, also known as dysbindin), whose longest protein isoform NP_115498.2 consists of 351 amino acids (~21.3 kd). Dysbindin binds to dystrobrevins in muscle and non-muscle cells and is also a component of biogenesis of lysosome-related organelles complex 1 (BLOC-1) [Falcón-Pérez et al 2002, Moriyama & Bonifacino 2002].

Abnormal gene product. Dermal fibroblasts from the Paraguayan boy with DTNBP1 deficiency showed markedly reduced dysbindin protein expression [Bryan et al 2017]. Further cellular studies on DTNBP1-deficient human cells are lacking.

References

Ammann S, Schulz A, Krageloh-Mann I, Dieckmann NM, Niethammer K, Fuchs S, Eckl KM, Plank R, Werner R, Altmuller J, Thiele H, Nurnberg P, Bank J, Strauss A, von Bernuth H, Zur Stadt U, Grieve S, Griffiths GM, Lehmberg K, Hennies HC, Ehl S. Mutations in AP3D1 associated with immunodeficiency and seizures define a new type of Hermansky-Pudlak syndrome. Blood 2016;127:997-1006

Badolato R, Prandini A, Caracciolo S, Colombo F, Tabellini G, Giacomelli M, Cantarini ME, Pession A, Bell CJ, Dinwiddie DL, Miller NA, Hateley SL, Saunders CJ, Zhang L, Schroth GP, Plebani A, Parolini S, Kingsmore SF. Exome sequencing reveals a pallidin mutation in a Hermansky-Pudlak-like primary immunodeficiency syndrome. Blood 2012;119:3185-7

Bryan MM, Tolman NJ, Simon KL, Huizing M, Hufnagel RB, Brooks BP, Speransky V, Mullikin JC, Gahl WA, Malicdan MC, Gochuico BR. Clinical and molecular phenotyping of a child with Hermansky-Pudlak syndrome-7, an uncommon genetic type of HPS. Mol Genet Metab 2017;120:378-83

Cullinane AR, Curry JA, Golas G, Pan J, Carmona-Rivera C, Hess RA, White JG, Huizing M, Gahl WA. A BLOC-1 mutation screen reveals a novel BLOC1S3 mutation in Hermansky-Pudlak Syndrome type 8 (HPS-8). Pigment Cell Melanoma Res 2012;25:584-91

Delevoye C, Heiligenstein X, Ripoll L, Gilles-Marsens F, Dennis MK, Linares RA, Derman L, Gokhale A, Morel E, Faundez V, Marks MS, Raposo G. BLOC-1 brings together the actin and microtubule cytoskeletons to generate recycling endosomes. Curr Biol 2016;26:1-13

Dell'Angelica EC, Shotelersuk V, Aguilar RC, Gahl WA, Bonifacino JS. Altered trafficking of lysosomal proteins in Hermansky-Pudlak syndrome due to mutations in the beta 3A subunit of the AP-3 adaptor. Mol Cell 1999;3:11-21

Di Pietro SM, Falcón-Pérez JM, Tenza D, Setty SR, Marks MS, Raposo G, Dell'Angelica GE. BLOC-1 interacts with BLOC-2 and the AP-3 complex to facilitate protein trafficking on endosomes. Mol Biol Cell 2006;17:4027–38

Enders A, Zieger B, Schwarz K, Yoshimi A, Speckmann C, Knoepfle EM, Kontny U, Muller C, Nurden A, Rohr J, Henschen M, Pannicke U, Niemeyer C, Nurden P, Ehl S. Lethal hemophagocytic lymphohistiocytosis in Hermansky-Pudlak syndrome type II. Blood 2006;108:81-7

Falcón-Pérez JM, Starcevic M, Gautam R, Dell'Angelica EC. BLOC-1, a novel complex containing the pallidin and muted proteins involved in the biogenesis of melanosomes and platelet-dense granules. J Biol Chem 2002;277:28191-9

Jessen B, Bode SF, Ammann S, Chakravorty S, Davies G, Diestelhorst J, Frei-Jones M, Gahl WA, Gochuico BR, Griese M, Griffiths G, Janka G, Klein C, Kögl T, Kurnik K, Lehmberg K, Maul-Pavicic A,

Mumford AD, Pace D, Parvaneh N, Rezaei N, de Saint Basile G, Schmitt-Graeff A, Schwarz K, Karasu GT, Zieger B, Zur Stadt U, Aichele P, Ehl S. The risk of hemophagocytic lymphohistiocytosis in Hermansky-Pudlak syndrome type 2. Blood 2013;121:2943–51

Li W, Zhang Q, Oiso N, Novak EK, Gautam R, O'Brien EP, Tinsley CL, Blake DJ, Spritz RA, Copeland NG, Jenkins NA, Amato D, Roe BA, Starcevic M, Dell'Angelica EC, Elliott RW, Mishra V, Kingsmore SF, Paylor RE, Swank RT. Hermansky-Pudlak syndrome type 7 (HPS-7) results from mutant dysbindin, a member of the biogenesis of lysosome-related organelles complex 1 (BLOC-1). Nat Genet 2003;35:84-9

Lowe GC, Sánchez Guiu I, Chapman O, Rivera J, Lordkipanidzé M, Dovlatova N, Wilde J, Watson SP, Morgan NV, UK GAPP collaborative. Microsatellite markers as a rapid approach for autozygosity mapping in Hermansky-Pudlak syndrome: identification of the second HPS7 mutation in a patient presenting late in life. Thromb Haemost 2013;109:766-8

Morgan NV, Pasha S, Johnson CA, Ainsworth JR, Eady RA, Dawood B, McKeown C, Trembath RC, Wilde J, Watson SP, Maher ER. A germline mutation in BLOC1S3/reduced pigmentation causes a novel variant of Hermansky-Pudlak syndrome (HPS8). Am J Hum Genet 2006;78:160-6

Moriyama K, Bonifacino JS. Pallidin is a component of a multi-protein complex involved in the biogenesis of lysosome-related organelles. Traffic 2002;3:666-77

Yousaf S, Shahzad M, Kausar T, Sheikh SA, Tariq N, Shabbir AS, University of Washington Center for Mendelian G, Ali M, Waryah AM, Shaikh RS, Riazuddin S, Ahmed ZM. Identification and clinical characterization of Hermansky-Pudlak syndrome alleles in the Pakistani population. Pigment Cell Melanoma Res 2016;29:231-5